

POSITION STATEMENT

See also COPD Supplement accompanying this issue

Postapproval Development Options in COPD: A Case Study in Value-Based Healthcare Systems

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Background: Research and development activities in an era of globalization encounter a mosaic of providers, products, services, and intermediaries; regulatory and other government institutions; and consumers. The introduction of novel therapeutics into this environment mandates research programs that are relevant to the registration process, payers and purchasers, transparent pricing, and rule-driven business practices, while providing data relevant to marketing initiatives internationally.

Objective: To outline an example for clinical development programs that incorporate the perspective of multiple stakeholders into a portfolio of study designs to provide optimal data platforms that can resonate with diverse recipients.

Discussion: A contract research organization directly involved in the design, execution, and analysis of clinical trials for new drugs and devices across pharmaceutical and biotechnology companies provides a unique perspective regarding opportunities and challenges within the international clinical research environment. Drs Murphy, Antonini, and Lai, representing Worldwide Clinical Trials, utilize chronic obstructive pulmonary disease as a demonstration project exploiting its prevalence, direct and indirect costs, and the rapid infusion/diffusion of innovative therapy into practice as a rationale for focus, and illustrate methods of informing registration and technology assessments during a prototypical development process.

Conclusion: By virtue of its chronicity, prevalence, and pattern of healthcare utilization, chronic obstructive pulmonary disease provides an ideal case for illustrating the application of clinical trial methodology that can facilitate data evaluation through the prism of multiple stakeholders. Adding an international dimension exacerbates system complexity and serves to illustrate the breadth of issues that can be addressed within this therapeutic area.

Am Health Drug Benefits.
2011;4(1):19-23
www.AHDBonline.com

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Research and development (R&D) activities in an era of globalization encounter a mosaic of providers, products, services, and intermediaries; regulatory and other government institutions; and consumers. Within the next 10 years, new product introductions within the United States and Western Europe in particular must navigate through a labyrinth of payers and purchasers, address the realities of transparent pricing and rule-driven business practices, and provide

research and data as a differentiator of sales and marketing initiatives. The information required for healthcare decisions will vary appreciably within this extended audience and is significantly influenced by the therapeutic area and local standards of care.

In this setting, the commercial viability of novel therapeutics—particularly for chronic illnesses that have established pharmacotherapy—is influenced by perceived value more than by mechanistic novelty. Review processes in the United Kingdom (ie, National Institute for Health and Clinical Excellence [NICE]), the German national system, and the Australian national formulary provide examples of oversight anticipated in many countries over the next decade.¹ Correspondingly, R&D activity supporting new product introductions must anticipate systems of oversight that mandate a stream of evidence confirming clinical utility in the presence of therapeutic uncertainty (eg, in

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the United States, the Centers for Medicare & Medicaid Services' coverage with evidence development).

Chronic obstructive pulmonary disease (COPD) provides a useful demonstration project of the methods by which R&D teams can address the perspective of multiple stakeholders in peri-approval research programs given its prevalence, direct and indirect costs, and the rapid infusion/diffusion of innovative therapy into practice. Adding an international dimension for consideration exacerbates system complexity and illustrates the breadth of issues that must be addressed within this therapeutic area.

An International Perspective

Pharmaceutical expenditure is a major concern in many European countries that use specific criteria in the process of identifying drugs that can be reimbursed by public funds, attempting to concentrate expenditures on key compounds that contribute to the treatment of illness deemed "serious." The method by which compound attributes are evaluated—cost-benefit assessment in Europe or comparative-effectiveness research in the United States—uses postapproval and peri-approval clinical research to generate evidence for clinical utility and cost-effectiveness in representative patients and in clinical practices to address key market access concerns.

For example, NICE has recommended additional research for a significant number of the drugs it appraised, including head-to-head comparisons (45%), investigation of the drug(s) in different patient populations (62%), and use of the drugs in typical clinical practice (87%).² Uncertainty around clinical effectiveness, typically resulting from inadequate study design given intended audiences or the use of inappropriate comparators and surrogate end points, has been identified as a key issue in coverage decisions in Britain, Australia, and Canada, although factors as diverse as competition and differences in risk tolerance can also have an impact on decisions.³

The Disease

COPD—an illness characterized by airflow limitation not fully reversible with bronchodilators because of progressive structural changes—is a major cause of chronic morbidity and mortality throughout the world, with growing impact on patients, families, healthcare systems, and society as a whole.⁴ In the European Union, the total direct costs of respiratory disease are estimated to be approximately 6% of the total healthcare budget, with COPD accounting for 56% (ie, 38.6 billion Euros) of this cost of respiratory disease.⁵

The guidelines for the management of COPD have

evolved over the past 10 years and are represented by the American Thoracic Society guidelines⁶ and the Global Initiative for Obstructive Lung Disease (GOLD).⁵ Both guidelines include clinical symptoms in addition to lung function measurements,^{5,6} acknowledging the reality that approximately 60% of primary care physicians never perform a lung function test on patients with respiratory symptoms.⁷

A Postapproval Clinical Program for COPD

The process of establishing an equilibrium between quality, access, and cost requires that peri-approval clinical research modifies any study objectives in a manner consistent with the audience intended for receipt of data. For example, managers of healthcare plans, hospitals, and pharmacy benefit management make decisions on formulary inclusion and limitations on utilization mainly based on data submitted during health technology assessments. Individuals making these assessments may not have an interest in understanding the subtlety of patient management for outcomes that are not directly relevant to their remit.

In this diverse setting, information on representative patients (including those with comorbidities and concomitant medications excluded during clinical development) and representative physicians (as opposed to clinical trialists) are weighed heavily. Comparative cost-effectiveness data are particularly useful as a means to inform formulary decisions and reimbursement guidelines.

As an example, medical directors of large international employers are interested in the impact of novel therapeutic interventions on workplace productivity and absenteeism when considering benefit coverage under employer-based plans.⁸ Direct loss of productivity occurs when people are sick and absent from work. Indirect loss of productivity (ie, presenteeism) can include additional time spent on tasks, decreased quality of work, impaired initiative, reduction in performance, decreased quantity of work completed, and limited social functioning with coworkers. All these outcomes are potentially measurable, as discussed below.

Although commercially insured employer-sponsored health plans may err on the side of caution by providing new medications to employees and their dependents regardless of expenditures, many employers are engaged in cost-shifting to employees and would be incentivized to favorably review data that could be used to promote healthier workforces to reduce healthcare expenditures. For example, given the impact of cigarette smoking on absenteeism and on presenteeism, clinical trial eligibility criteria during a registration program that also permitted evaluation of the impact of smoking with or without novel medication on healthcare utilization and work-

place productivity will be far more important than trials that solely monitor medical respiratory outcomes (eg, forced expiratory volume in 1 second [FEV₁]). These data permit modeling of the annual cost burden per employee that may be associated with new product introduction.

A Portfolio of Design Options

Depending on the scope and objectives (eg, safety, efficacy, quality-of-life outcomes) for postmarketing clinical studies in COPD, different study designs may be appropriate, including interventional or observational studies using randomized versus nonrandomized designs, with a prospective or a retrospective focus.

Randomized Clinical Trials

The use of randomization minimizes bias regarding comparability of treatment groups, because known and unknown prognostically important variables are allocated between treatment groups randomly. Individual patient–randomized versus cluster-randomized designs (eg, at this level of clinical practice) permit inferences under assumptions that differences detected in outcomes reflect random variation plus the effect of intervention.

Benefits include the ability to capture multiple outcomes of interest spanning domains of safety and efficacy (eg, FEV₁), patient-reported outcomes, and healthcare utilization (eg, hospitalization for COPD exacerbation)—critically parsing the impact of an intervention using methods that have universal acceptance biostatistically. An enabling technological infrastructure for randomization and data acquisition with minimal costs from direct site monitoring reduces concerns regarding excessive operational overhead.

Registry/Prospective Observational Studies

With broad eligibility criteria and unrestricted site participation, this approach is a “hypothesis-generating exercise” that can include large and diverse groups of patients. Treatment patterns reflect “real-life” situations—everyday clinical decision-making that can inform subsequent controlled studies in patients with comorbidities and concomitant medications that may have been excluded from a registration program. Lack of randomization—and the limitation in potential inferences—can be partially addressed through analytic techniques, such as propensity score analyses, and has been utilized in COPD in the evaluation of healthcare utilization and costs.⁹ The range of quantitative study designs not including randomization in quality improvement research, for example, includes stepped wedge designs, time-series designs, and controlled or uncontrolled before-after studies that create a body of evidence for practical decision-making purposes.¹⁰

In this setting, electronic data acquisition is mandatory coupled with a “user-friendly” web-based “wrap-around” interface, permitting unencumbered access to an electronic data capture platform by all participants. During this process, access to electronic health records using a limited data set is a laudable objective with technological and privacy considerations acknowledged.¹¹ Efficient use of health information technology and interoperable data in which a single point of entry can provide research and clinical information has been the subject of key initiatives.¹² When fully articulated, electronic data capture methodology may transform every physician–patient interaction into an opportunity for research.

Particularly attractive are studies placed in a “closed environment” in which all transactions can be monitored (eg, physician visits, laboratory tests, pharmacy claims, and specialist contact). Although available in the United States (eg, Geisinger Clinic, Kaiser Permanente) and applied in COPD within the Veterans Affairs healthcare system,¹³ this type of setting is more difficult to replicate in European countries. Patient registries that use observational study methods to evaluate outcomes provide an alternative.¹⁴ For example, similar to techniques employed with antihypertensive medications,¹⁵ an investigation of the influence of prescription cost-sharing on medication refill persistence may be entertained by evaluating 2 therapeutic classes of bronchodilators that are differentially reimbursed in an observational trial.

Patient Population

COPD severity and comorbidity significantly modify implications extracted from any research. Patients with moderate-to-severe COPD (GOLD II and III) represent the majority of patients with COPD requiring continuous treatment. For example, in the Social Impact of Respiratory Integrated Outcomes (SIRIO) study of 748 Italian patients, in which COPD severity levels were based on the GOLD 2001 guidelines, 24.2% of patients were classified as mild, 53.7% moderate, and 16.8% severe.¹⁶ Because patients with COPD tend to be older (eg, the mean age was 70.3 years in the SIRIO study),¹⁶ comorbid conditions are frequent, including common pathway comorbidities (ie, smoking-related diseases such as ischemic heart disease); complicating comorbidities (ie, pulmonary hypertension); coincidental morbidities related to aging (ie, depression or diabetes); and intercurrent comorbidities (ie, upper respiratory infections) occurring during the course of observation. In comparative trials, all modifying elements need to be either constrained by design or randomly allocated, or adjusted between groups analytically to permit appropriate between-group comparisons.

Patients with COPD and these comorbidities are often not eligible for participation in clinical trials, and would therefore not be represented sufficiently in a typical registration dossier. For example, in a study conducted in Norway, only 17% of the patients with COPD were estimated to meet the inclusion criteria used in clinical trials for moderate-to-severe COPD.¹⁷ In addition, comorbidities may create problems of conflicting therapies—for example, evaluation of corticosteroids in patients with COPD and hypertension or diabetes, or the impact of beta-blockers in COPD patients who are at high cardiovascular risk. Because comorbidities and concomitant therapy drive healthcare utilization in many diagnoses, however, generating data in such patients would be very relevant to organizations that must make coverage decisions.

Typology of Sites

Primary care versus specialized centers for respiratory disorders offer intriguing insights regarding the impact of the clinical setting on health outcomes. In primary care centers, the management of patients with COPD may be tangentially related to guidelines, although very representative of the “real-world” practice. The benefits include access to physicians who provide care for the majority of patients with COPD. The disadvantages include the inconsistency among private providers regarding diagnosis and treatment,⁷ despite the high regard in which COPD guidelines are held.¹⁸ For example, in the primary care setting, one obstacle for evaluating the efficacy of the therapy using “gold standard” methodology is represented by limited access to spirometry equipment.

In specialized centers for respiratory disorders, the management of patients with COPD may not be representative of the population that will eventually be covered, although procedures and medication use by specialists better adhere to guidelines. Benefits to clinical research in this setting include staffing and infrastructure necessary to conduct sophisticated controlled clinical trials, including, but not limited to, high-quality spirometry. Disadvantages are primarily related to the selection bias associated with tertiary care centers, because only the most severe or intractable COPD population is referred to these sites. A retrospective and prospective cost-of-illness study in France provides a model approach to the evaluation of disease impact in COPD, including general practitioners and lung specialists.¹⁹

Outcome Measures

Although FEV₁ measurement is a standard for the evaluation of respiratory function in COPD, the absence of high-quality spirometry in the primary care setting

can be attenuated by the use of a peak flow meter for lung function. Alternatively, protocol design with clinical symptoms as primary outcomes can be particularly useful. For example, of the chronic symptoms characteristic of COPD (ie, cough, sputum, dyspnea), dyspnea is the symptom that interferes most with a patient’s daily life and health status. Therefore, it is important to explore the impact of dyspnea and other chronic symptoms on daily activities and work. Dyspnea and quality-of-life indices qualify the disease burden of COPD and patients’ perceived quality of life, such as the British Medical Research Council questionnaire (for daily activities); the Clinical COPD Questionnaire (for COPD-related symptoms, functional status, and mental health); or the St. George’s Respiratory Questionnaire (for impaired health; and perceived well-being).

Event studies are particularly useful for reimbursement purposes, because they reflect the healthcare utilization (eg, hospitalization) and cost-effectiveness of therapies that may be anticipated with chronic medication use. However, the duration of an investigation would extend to 1 year if exacerbation is included as an end point compared with 12 weeks if FEV₁ is the primary end point. Therefore, the proposed study design would require a longer horizon for data accrual if exacerbation rates are requirements for health technology decisions.

Active Comparator and Concomitant Medications for COPD

Given the standard of care represented by tiotropium/ipratropium, fixed combinations of inhaled corticosteroids (ICSs) and long-acting beta-agonists (LABAs) or ICS plus LABA combined with tiotropium/ipratropium provide optimal therapeutic combinations for study. As a result of its long mechanism of action, tiotropium is the antimuscarinic drug of choice for patients with COPD in the European Union, and it serves as a standard comparator for any antimuscarinic drugs or other bronchodilators.

For example, tiotropium was the drug of choice for comparison in the recent phase 3 Study to Compare the Lung Effect of Indacaterol and Tiotropium in Chronic Obstructive Pulmonary Disease (INTENSITY),²⁰ even though the drug under evaluation is of a different pharmacologic class (ie, a novel LABA) and can possibly be used in combination with tiotropium. The rationale of this head-to-head comparison is that bronchodilator medications are central to symptom management in COPD, and the choice between a LABA or an anticholinergic depends on individual response in terms of symptom relief. Because of the prevalent use of a fixed combination of ICS plus LABA in this patient population for randomized clinical trials, it may be worthwhile

to permit stable dosage of the ICS (if used) as background therapy.

Use of Inhaler Devices

For COPD drugs delivered through inhalation devices, it is important to evaluate ease of use and patients' preference of different devices, because these variables are determinants of medication adherence and success of COPD therapy.²¹ For example, the use of a multidose dry powder inhaler may be more convenient and provide improved drug deposition compared with that of a different device, with an equivalent drug product. Patients' preference and adherence to therapy may be included as secondary end points. Cost-effectiveness can be discerned through the use of a variety of analytic techniques represented by the first published study comparing cost-effectiveness of an ICS, a LABA, and a combination of both agents from the perspective of US healthcare payers.²²

Reviewing the implications of this paradigm through a prism of international clinical development is particularly useful as systems for vetting clinical trial results that have been used as a platform for determining product access and reimbursement.

Conclusions

The introduction of the Patient Protection and Affordable Care Act in the United States in 2010 has prompted a reevaluation of research priorities across therapeutic areas. Reviewing the implications of this paradigm through a prism of international clinical development is particularly useful as systems for vetting clinical trial results that have been used as a platform for determining product access and reimbursement. Much is known regarding the character and extent of data required for consideration. By virtue of its chronicity, prevalence, and pattern of healthcare utilization, COPD provides an ideal demonstration case illustrating the application of innovative clinical trial methodology that could service the perspectives of multiple stakeholders. ■

Author Disclosure Statement

Dr Murphy, Dr Antonini, and Dr Lai are employees of Worldwide Clinical Trials, an international, full-service con-

tract research organization that specializes in clinical trial research activities in support of drug development by pharmaceutical companies. As part of their primary business activities, relationships exist with multiple (more than 100) pharmaceutical companies. These activities include consultation regarding design, execution, analysis, and interpretation of clinical trials within the pharmaceutical and biotechnology industry. None of the authors receives any personal financial remuneration for any drug product or device.

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